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PD-L1 expression predicts longer disease free survival in high risk head and neck cutaneous squamous cell carcinoma

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PD-L1 expression predicts longer disease free survival in high risk head and neck cutaneous squamous cell carcinoma

Abstract

Programmed cell death (PD-1) and its ligand (PD-L1) inhibitors have shown clinical response in many tumours. PD-L1 data are limited in head and neck cutaneous squamous cell carcinoma (HNcSCC) and no clinical trials of PD-1/PD-L1 inhibitors are published. We performed PD-L1 immunohistochemistry on 74 cases of high risk HNcSCC with 38 matched metastases and evaluated clinicopathological associations, prognostic significance and heterogeneity in matched metastases. We observed PD-L1 expression in >5% of primary tumour cells in 29 cases (39.2%), primary tumour infiltrating lymphocytes (TILs) in 40 cases (70.2%), metastatic tumour cells in 15 cases (39.5%), and metastatic TILs in 18 cases (47.4%). PD-L1 expression in >5% of primary tumour cells was associated with an inflammatory phenotype ($p = 0.04$), and in primary TILs with clear margins ($p = 0.05$). PD-L1 expression in >5% of primary tumour cells ($p = 0.01$), primary TILs ($p = 0.001$), and metastatic TILs ($p = 0.02$) was associated with improved disease free survival. PD-L1 expression in >5% of tumour cells was heterogeneous between primary and metastatic tumours in 13 cases (34.2%). PD-L1 expression is common in HNcSCC supporting the rationale for a clinical trial of PD-1/PD-L1 inhibitors. PD-L1 expression in tumour cells or TILs predicts longer disease free survival and demonstrates temperospatial heterogeneity.

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PD-L1 Expression Predicts Improved Disease Free Survival in High Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Running title: PD-L1 predicts improved DFS in HNcSCC

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Abstract

Immune checkpoint inhibitors targeting programmed cell death ligand (PD-1) and its ligand (PD-L1) have shown clinical response in a range of tumors and the associated literature is rapidly evolving. There is, however, limited data regarding the immunohistochemical expression of programmed cell death ligand 1 (PD-L1) in head and neck cutaneous squamous cell carcinoma (HNcSCC) and there are no published clinical trials for the use of PD-1/PD-L1 inhibitors. Therefore we aimed to evaluate PD-L1 expression in high risk HNcSCC including its association with clinicopathological factors, its prognostic significance, and heterogeneity of expression in matched metastases. Clinicopathological review and PD-L1 immunohistochemistry was performed on 74 cases of high risk HNcSCC including 38 patients with metastases. PD-L1 expression was assessed in both the tumor cells and the tumor infiltrating lymphocytes (TILs). Disease free survival according to PD-L1 expression and heterogeneity between primary HNcSCC and their metastases were analysed. PD-L1 staining in >5% of primary HNcSCC tumor cells was observed in 29 cases (39.2%) and in TILs in 40 cases (70.2%). PD-L1 staining in >5% of metastatic HNcSCC tumor cells was observed in 15 cases (39.5%) and TILs in 18 cases (47.4%). PD-L1 expression of >5% was associated with an inflammatory phenotype for primary tumor cells (p=0.04) and clear margins for primary TILs (p=0.05). PD-L1 expression in primary tumor cells (p=0.01), primary TILs (p=0.001), and metastatic TILs (p=0.02) was associated with improved disease free survival. Heterogeneity in PD-L1 expression between primary and metastatic tumors was observed in 13 cases (34.2%). PD-L1 expression is common in HNcSCC, is generally associated with an inflammatory phenotype and improved disease free survival, however its expression varies between primary and metastatic tumors. This provides support for a clinical trial of PD-1/PD-L1 inhibitors in HNcSCC.

Immune checkpoints including Programmed Cell Death-Ligand 1 (PD-L1) and its receptor (PD-1) are inhibitory pathways that suppress host T cells and moderate the physiological immune response to limit tissue damage and maintain self-tolerance.[1] Many of these checkpoints are ligand-receptor interactions and therefore amenable to pharmacological modulation that can reactivate T cells to eliminate tumor cells.[1] The interaction between PD-L1 and PD-1 suppresses the immune system by transducing an inhibitory signal on T cell proliferation, cytokine production and cytotoxic function.[2] Clinical data for PD-1/PD-L1 inhibitors have shown response rates ranging from 10-50% in metastatic melanoma, non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, metastatic urothelial carcinoma, ovarian cancer, haematological malignancies and head and neck squamous cell carcinoma.[3] There is, however, no data regarding the prognostic significance of PD-L1 expression and no published clinical trials evaluating PD-1/PD-L1 inhibitors in high risk head and neck *cutaneous* squamous cell carcinoma (HNcSCC).

Cutaneous squamous cell carcinoma (cSCC) is one of the most common and expensive malignancies and the incidence continues to rise with the aging population.[4,5] The vast majority of cases occur on the UV-exposed head and neck region.[6] Although most are localized and curable, advanced disease requires radical surgery and post-operative radiotherapy leading to significant functional morbidity.[7] Given this rising burden of disease and the limited systemic therapeutic options for advanced cSCC, novel treatment options such as immune checkpoint inhibitors need to be explored.[8]

A recent meta-analysis demonstrated that immunohistochemical expression of PD-L1 in tumor cells was associated with clinical response to PD-1/PD-L1 inhibitors in metastatic

melanoma and non-squamous NSCLC but not in renal cell carcinoma or squamous NSCLC.[9] Similarly, Herbst et al have shown an association between clinical response to PD-1/PD-L1 blockade and PD-L1 expression in tumor cells and tumor infiltrating lymphocytes (TILs) across a range of tumor types.[10] Data regarding PD-L1 expression in cSCC is just emerging, being limited to two cohort studies, and represents an area of need given the dearth of therapeutic options for advanced, unresectable HNcSCC.[11,12] This study evaluates PD-L1 expression in primary and metastatic tumor cells and TILs. The association of PD-L1 expression with conventional prognostic factors and survival has been evaluated. Heterogeneity in the expression of PD-L1 between primary carcinomas and their metastases has been investigated.

Materials and methods

74 patients with high risk HNcSCC, [13]and detailed clinicopathological information were identified from the Sydney Head and Neck Cancer Institute database (1997-2015) after approval from the institution's human research ethics committee. Of these 74 patients, 35 had high risk primary HNcSCC without nodal metastases and the remaining 39 had metastases to cervical or intraparotid lymph nodes. Tumor-containing archival formalin fixed paraffin embedded tissue blocks were retrieved for all 74 primary specimens and 38 of 39 metastatic specimens.

Clinical and follow up data:

Data on patient demographics, post-operative adjuvant therapy, local failure, regional failure, distant metastases and survival were obtained.

Histopathological review:

The archival slides from all 74 primary tumors and 38 metastases were reviewed for tumor size, depth of invasion, tumor differentiation, margins of resection, lymphovascular and perineural invasion, and for evaluation of tumor infiltrating lymphocytes. All tumors were staged using the 7th edition of the American Joint Committee on Cancer Cancer Staging Manual pTNM staging system for primary cSCC.[13]

Quantification of tumor infiltrating lymphocytes (TILs):

TILs at the infiltrative front of the tumor were quantified as 0-3 as per Busam *et al* for primary cutaneous melanoma as well as Klintrup *et al* and Huh *et al* for colorectal carcinoma as follows: 0: no lymphocytes invading tumor; 1: patchy infiltration by occasional lymphocytes; 2: lymphocytes partially or completely surrounding of tumor islands with destruction of tumor islands focally; 3: diffuse, thick, band-like lymphocytic infiltration with destruction of tumor islands.[14-16]

Immunohistochemistry:

Whole fixed formalin paraffin embedded tissue blocks were cut at 4µm onto SuperFrost Plus glass slides. Immunohistochemistry was performed utilizing Leica Biosystems Bond III autostaining with high pH target retrieval buffer (Leica Biosystems, ER2 #AR9640) as per the manufacturer's instructions. The primary antibody against PD-L1 (SP263 RbmAb Ventana Predilute #07494190001) was incubated for 30 minutes at room temperature and visualized using the Bond Polymer Refine Detection Kit (Leica Biosystems #D59800) as per the manufacturer's instructions.

PD-L1 staining:

PD-L1 staining intensity was quantified in both cSCC and TILs as follows: no staining (0+); weak but perceptible and convincing membranous staining (1+); moderate membranous staining (2+); strong membranous +/- cytoplasmic staining (3+) (Figure 1).

Statistical analysis:

Statistical analysis was performed using Stata version 11.2 (Statacorp, TX). Categorical data was analysed using the chi-square test and continuous data using the two-sample T test. Hazard rations for clinicopathological variables were calculated using the Cox proportional hazards model. Disease-free survival was calculated from the date of surgery to date of first disease recurrence, or death. Survival curves were generated using the Kaplan-Meier method. p values less than 0.05 were considered statistically significant. PD-L1 staining percentage was initially analysed as a continuous variable in tumor cells and in TILs and then subsequently a statistically significant and clinically useful cut-off (>5%) was used for further analysis.

Results

Cohort characteristics:

The cohort included 64 males and 10 females (M:F = 6.4:1) with a median age of 69.9 years (range 34-100 years). Adjuvant radiotherapy was administered to 23 patients (31.5%), including 10 without metastases and 13 with metastases. Adjuvant chemotherapy (carboplatin) was administered to two patients (2.7%) without metastases. The median follow-up time was 2.2 years (range 0.1-7.9 years) with 32 deaths (43.2%), including six attributed to HNcSCC (Table 1).

PD-L1 expression:

In primary HNcSCC (n=74), PD-L1 expression was seen in tumor cells in 39 cases (52.7%); of these, 29 cases (39.2%) demonstrated PD-L1 expression in >5% of the cells. In cases where TILs were present (n=57), PD-L1 expression was seen in TILs in 53 cases (93%); of these, 40 cases (70.2%) demonstrated PD-L1 expression in >5% of the cells.

In metastatic HNcSCC (n=38), PD-L1 expression was seen in tumor cells in 17 cases (44.7%); of these, 15 cases (39.5%) demonstrated PD-L1 expression in >5% of the cells. PD-L1 expression was seen in TILs in 28 cases (73.7%); of these, 18 cases (47.4%) demonstrated PD-L1 expression in >5% of the cells (Table 2).

Association between PD-L1 expression and clinicopathological variables:

In primary HNcSCC, PD-L1 expression in >5% of tumor cells was associated with the presence of TILs (an inflammatory phenotype) (p=0.04). In primary HNcSCC, PD-L1 expression in >5% of TILs (excluding cases with absent TILs) was associated with clear margins (p=0.05). PD-L1 expression in primary and metastatic tumor cells and TILs was not associated with any other clinicopathological feature or conventional prognostic factors such as tumor size or lymphovascular invasion in this immunotherapy naïve cohort. There was weak evidence for an association with PNI (p=0.10 for both the primary tumor cells and TILs) (Table 3).

PD-L1 expression and survival:

In primary HNcSCC, PD-L1 expression in >5% of tumor cells (p=0.01, HR=0.43, CI=0.23-0.83) and in >5% of TILs (p=0.001, HR=0.30, CI=0.15-0.60) was associated with improved disease

free survival (DFS) (Table 4, Figure 2A). There was strong evidence for strong staining intensity (2+-3+) of PD-L1 in TILs being associated with improved DFS (P=0.01, HR=0.41, CI=0.20-0.84) but only weak evidence for strong staining intensity of PD-L1 in tumor cells being associated with improved DFS (p=0.09, HR=0.52, CI=0.25-1.10).

In metastatic HNcSCC, neither PD-L1 expression in tumor cells nor increasing staining intensity of PD-L1 were associated with DFS (p=0.40 and p=0.64 respectively). In contrast, PD-L1 expression in >5% of TILs (p=0.02, HR=0.35, CI=0.14-0.87) and strong staining intensity of PD-L1 in TILs (p=0.04, HR=0.35, CI=0.13-0.95) were both associated with improved DFS (Table 4, Figure 2B and 2C).

Heterogeneity between primary HNcSCC and their metastases:

Of 38 pairs of primary specimens and their metastases, discordant PD-L1 expression of tumor cells was seen in 13 (34%) cases, of which five demonstrated lack of PD-L1 expression and eight demonstrated presence of PD-L1 expression in the metastases as compared to their primary cancers (Table 5).

Discussion

This study is one of the first to evaluate the frequency and clinicopathological associations of PD-L1 expression in immunotherapy naïve high risk HNcSCC and contributes four main findings to the evolving data regarding PD-L1: (1) PD-L1 expression is common in HNcSCC tumor cells and TILs in both primary and metastatic specimens; (2) PD-L1 expression in primary tumor cells, primary TILs, and metastatic TILs is associated with improved DFS; (3) PD-L1 expression in primary tumor cells is associated with an inflammatory phenotype; and

(4) PD-L1 expression of tumor cells shows heterogeneity between primary and metastatic specimens; furthermore unlike their primary counterpart, PD-L1 expression in metastatic tumour cells is not associated with survival.

In the current study, PD-L1 expression in >5% of tumor cells was seen in 39 of the primary cases (52.7%) using the SP263 rabbit monoclonal antibody. The literature regarding PD-L1 expression is fraught with variable rates of PD-L1 expression that cannot be compared across studies due to the different antibody clones and cut-offs that have been employed.[3,17,18] For example, Slater and Googe report a 70% incidence of PD-L1 expression in primary high-risk cSCC in a cohort of 20 cases with SP142 clone and a cut-off of ≥1%; on the other hand Schaper *et al* report a 10.3% incidence of PD-L1 expression in primary cSCC, without risk-stratification, in a cohort of 68 cases using the E1L3N clone and a cut-off of ≥5%.[11-12] While correlation with clinical response to PD-1/PD-L1 inhibitors is yet to be determined, the SP263 antibody was recently found by Smith et al to be a superior assay, and hence the SP263 antibody was selected for this study.[19] Our cut-off of 5% was selected because it was associated with a statistically significant improvement in DFS in this immunotherapy naïve cohort. Notably, this cut-off has also been shown in a range of tumors to predict response to PD-1/PD-L1 inhibitors.[9] Nevertheless, further data, in particular response rates to PD-1/PD-L1 inhibitors, are required from the various tumor-specific trials before the clinical validity of a given antibody clone or cut-off can be determined.

The prognostic significance of PD-L1 expression in tumor cells of primary HNcSCC has not previously been described. As an immunosuppressive molecule promoting tumor evasion, the increased expression of PD-L1 intuitively should result in a worse prognosis as is

documented in gastric, breast, renal, and pancreatic cancer.[20-23] However, improved prognosis has been associated with PD-L1 expression in metastatic melanoma, Merkel cell carcinoma, HPV-associated head and neck SCC, mismatch-repair-proficient colorectal cancer, NSCLC, and small cell lung cancer.[24-29] One potential answer to this paradox is that the PD-L1 molecule is inducible by local inflammatory factors such as interferon-gamma in the tumor microenvironment, hence its expression could reflect an active, endogenous, anti-tumoral immune response.[24,30] This may also explain the strong association of survival with TILs in both the primary and metastatic HNcSCC compared with the tumor cells. In contrast to tumor cells, there is limited data regarding the prognostic value of PD-L1 expression in TILs, however a similar effect of improved prognosis with PD-L1 expression in TILs was reported in spinal chordoma, ovarian high grade serous carcinoma, and urothelial carcinoma.[31-33] Thus our data suggest that PD-L1 is biologically relevant in the HNcSCC tumor microenvironment, supporting a potential therapeutic role for PD-1/PD-L1 inhibitors.

PD-L1 expression in HNcSCC tumor cells was associated with an inflammatory phenotype, as has also been observed in the two other documented series of PD-L1 expression in cSCC.[11-12] A similar association between PD-L1 expression in tumor cells and the presence of TILs has been reported in melanoma, NSCLC, breast cancer, and oral SCC.[24,28,34,35] This association may reflect an endogenous TIL-mediated anti-tumoral response rather than a tumor-driven pathway for immune evasion, which would be consistent with improved survival described above.[36] PD-L1 expression in tumor cells was not found to be statistically associated with any other clinicopathological variables in this immunotherapy naïve cohort. Interestingly, PD-L1 expression in TILs was associated with a lower incidence of involved margins. A similar association has been described in PD-L1 expression of CD99+ sarcoma tumor cells.[37] The

reason for this correlation is unclear, although it supports the possibility that PD-L1 positive TILs may be associated with a less infiltrative growth pattern and a more effective tumor control.

Our data demonstrate heterogeneity in PD-L1 expression in primary HNcSCC and their metastases in 34% of cases. Unlike their primary counterparts, the PD-L1 expression in metastatic tumors was not associated with survival. A similar spatial and temporal heterogeneity has been described in other malignancies such as clear cell renal carcinoma, melanoma, and lung cancer.[38-41] This finding has implications for designing clinical trials and for retesting of metastatic neoplasms, which may be more or less accessible than their primary counterparts. This is particularly relevant for cSCC as the histologic material of the primary site may not be easily available for testing in many metastatic cases.

Currently, there are no tumor-specific trials of PD-1/PD-L1 inhibitor in *cutaneous* SCC. In a review article of multiple tumor types, Patel and Kurzrock suggest that tumor types classically responding to PD-1/PD-L1 inhibitors tend to have higher rates of PD-L1 expression by immunohistochemistry than tumor types with typically poor responses.[18] This supports the rationale for a trial of PD-1/PD-L1 inhibitors in HNcSCC. The argument is strengthened by several inherent characteristics of cSCC including its high mutational burden and its immunogenic nature, where immunosuppression confers a 65 times increased risk of developing cSCC in solid organ transplant recipients; both of which are described as being positively associated with response to PD-1/PD-L1 inhibitors.[42-45] Furthermore, murine studies and six independent case reports have shown responses to PD-1/PD-L1 inhibitors in unresectable cSCC ranging from disease stabilisation to complete response.[46-49]

In conclusion, this is the largest HNcSCC tumor series to date to evaluate PD-L1 expression and the first to report an association with survival. PD-L1 expression is common in tumor cells and TILs and provides further evidence for a clinical trial of PD-1/PD-L1 inhibitors in HNcSCC. We also demonstrate that PD-L1 expression in >5% of primary tumor cells, primary TILs, and metastatic TILs is associated with an improved DFS in HNcSCC.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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Figure legends

Figure 1 – Immunohistochemistry for PD-L1 by intensity of staining (A-D): PD-L1 staining intensity 1+ in tumor cells (A); PD-L1 staining intensity 2+ in tumor cells (B); PD-L1 staining intensity 3+ in tumor cells (C); PD-L1 staining intensity 3+ in tumor infiltrating lymphocytes (D).

Figure 2 – Kaplan-Meier analysis of disease free survival and PD-L1 (A-C): Disease free survival by PD-L1 percentage in primary tumor cells (A); Disease free survival by PD-L1 percentage in primary TILs (B); Disease free survival by PD-L1 percentage in metastatic TILs (C).

Tables

Table 1 – Cohort characteristics		
Mean age (range)		69.9 years (34 – 100)
Sex	Male	64 (86.5%)
	Female	10 (13.5%)
Mean tumor diameter (range)		32.7mm (3 – 160mm)
Mean tumor thickness (range)		14.4mm (0.3 – 70mm)
Perineural invasion		37 (50%)
Lymphovascular invasion		13 (17.6%)
Tumor infiltrating lymphocytes	Present	57 (77%)
	1- Patchy	32 (43.2%)
	2 - Moderate	19 (25.7%)
	3 - Diffuse	6 (8.1%)
T category	T1	11 (14.9%)
	T2	46 (62.2%)
	T3	4 (5.4%)
	T4	13 (17.6%)
Node status	N0	35 (47.3%)
	N1	12 (16.2%)
	N2a	3 (4.1%)
	N2b	22 (29.7%)
	N2c	2 (2.7%)
Differentiation	Well	5 (6.8%)

	Moderate	47 (63.5%)
	Poor	22 (29.7%)
Margins	Clear	21 (28.4%)
	Close	25 (37.8%)
	Involved	28 (37.8%)
Metastases	Present	39 (52.7%)[#]
Follow up	Mean (years)	2.2 years (0.1 – 7.9)
[#]*One metastatic specimen did not undergo PD-L1 assessment*		

Table 2 – Rates of PD-L1 staining intensity and PD-L1 staining percentage					
		Primaries		Metastases	
		Tumor cells (n=74)	TILs (n=57)*	Tumor cells (n=38)	TILSs (n=38)
PD-L1 staining percentage	0% 1-5% >5%	35 (47.3%) 10 (13.5%) 29 (39.2%)	4 (7.0%) 13 (22.8%) 40 (70.2%)	21 (55.3%) 2 (5.3%) 15 (39.5%)	10 (26.3%) 10 (26.3%) 18 (47.4%)
PD-L1 staining intensity	0+ 1+ 2+ 3+	35 (47.3%) 11 (14.9%) 23 (31.1%) 5 (6.8%)	4 (7.0%) 7 (12.3%) 35 (61.5%) 11 (19.3%)	21 (55.3%) 6 (15.8%) 6 (15.8%) 5 (13.2%)	10 (26.3%) 8 (21.1%) 16 (42.1%) 4 (10.5%)
**TILs were observed for PD-L1 assessment in 57 cases only*					

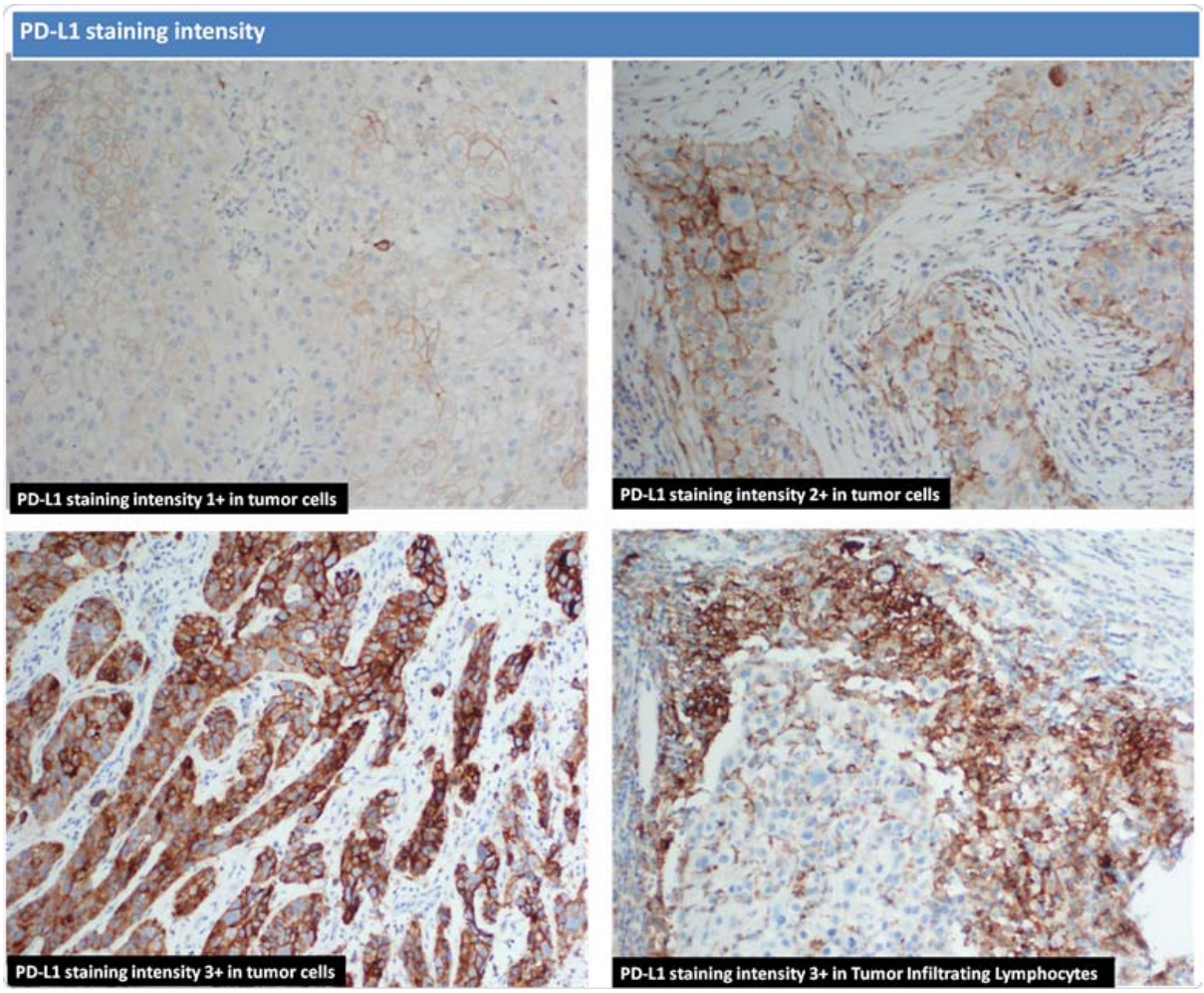
Table 3 – Associations between PD-L1 staining percentage >5% and clinicopathological variables in primary HNcSCC specimens (n=74)					
Continuous variables		Tumor cells	p	TILs	p
Mean age (years)	PD-L1 0-5% PD-L1 >5%	68.8 71.7	0.44	69.6 70.2	0.88
Mean tumor diameter (mm)	PD-L1 0-5% PD-L1 >5%	33.1 32.0	0.86	34.9 31.3	0.59
Mean tumor	PD-L1 0-5%	15.0	0.54	16.4	0.26

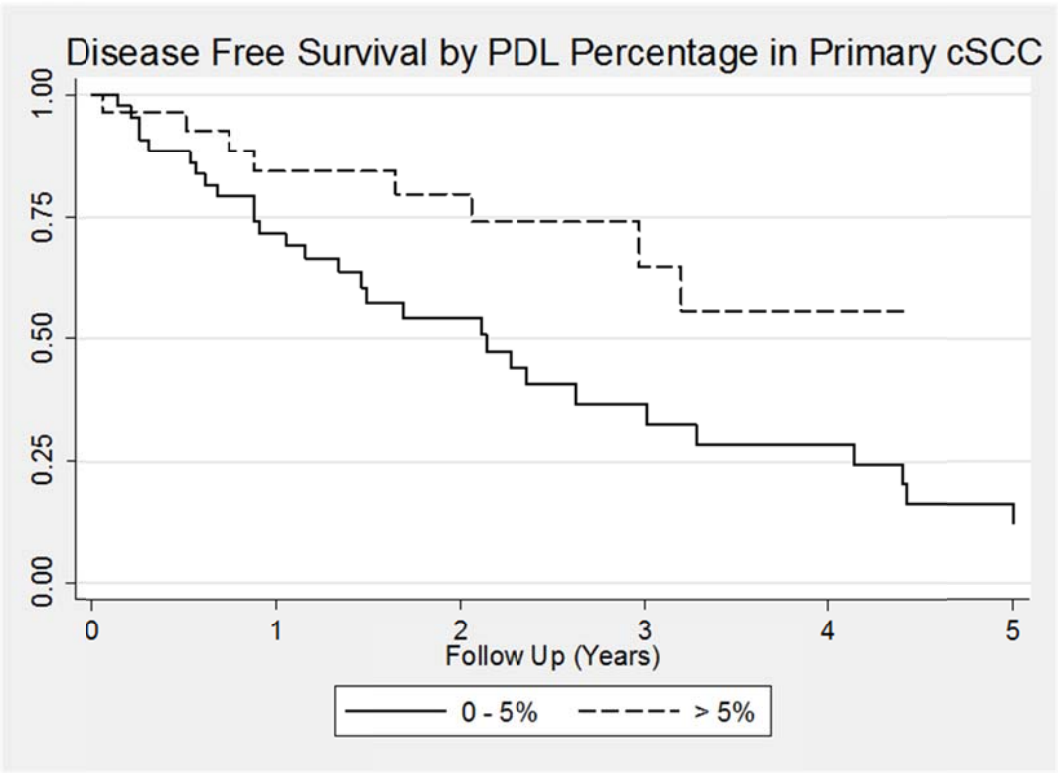
thickness (mm)	PD-L1 >5%	13.0		12.8	
Categorical variables		PD-L1 staining percentage > 5%			
		Tumor cells	p	TILs	p
Gender	Male Female	37.5% 50.0%	0.45	62.5% 50.0%	0.45
T category	T1/2 T3/4	43.9% 23.5%	0.13	61.4% 58.8%	0.85
Node / Metastasis status	Negative Positive	40.0% 38.5%	0.89	65.7% 56.4%	0.41
Tumor infiltrating lymphocyte	Absent Present	17.7% 45.6%	0.04	N/A 70.2%	N/A
Margins	Clear Involved	45.7% 28.6%	0.14	69.6% 46.4%	0.05*
Differentiation	Well Moderate Poor	20.0% 42.6% 36.4%	0.59	100% 61.7% 50.0%	0.12
Perineural invasion	Absent Present	48.7% 29.7%	0.10	70.3% 51.4%	0.10
Lymphovascular invasion	Absent Present	37.7% 46.2%	0.57	60.7% 61.5%	0.95

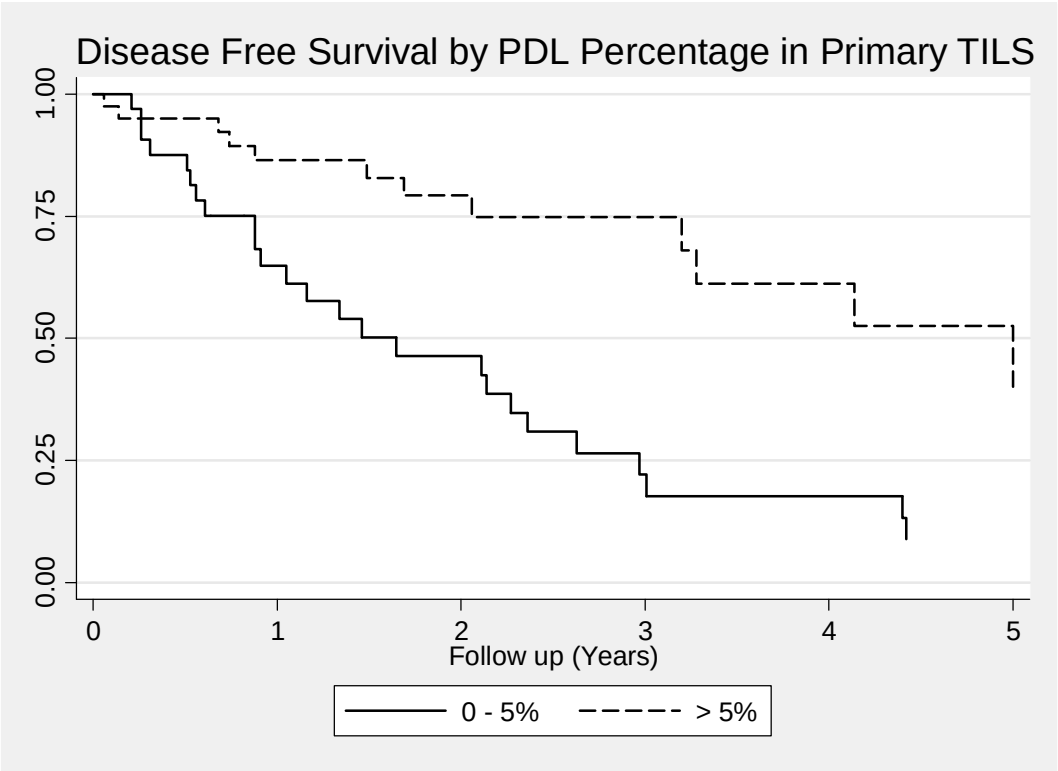
Table 4 – Disease free survival and PD-L1 expression in HNcSCC				
	Primaries		Metastases	
	Tumor cells (n=74)	TILs (n=57)	Tumor cells (n=38)	TILs (n=38)
PD-L1 staining percentage	> 5% vs. 0-5% P = 0.01* HR = 0.43 CI = 0.23-0.83 *See graph 1*	> 5% vs. 0-5% P = 0.001* HR = 0.30 CI = 0.15-0.60 *See graph 2*	> 5% vs. 0-5% P = 0.40 HR = 1.45 CI = 0.61-3.43	> 5% vs. 0-5% P = 0.02* HR = 0.35 CI = 0.14-0.87 *See graph 3*
PD-L1 staining intensity	2/3+ vs. 0+ P = 0.09 HR = 0.53 CI = 0.25-1.10	2/3+ vs. 0+ P = 0.01* HR = 0.41 CI = 0.20-0.84	2/3+ vs. 0+ P = 0.64 HR = 1.25 CI = 0.48-3.24	2/3+ vs. 0+ P = 0.04* HR = 0.35 CI = 0.13-0.95

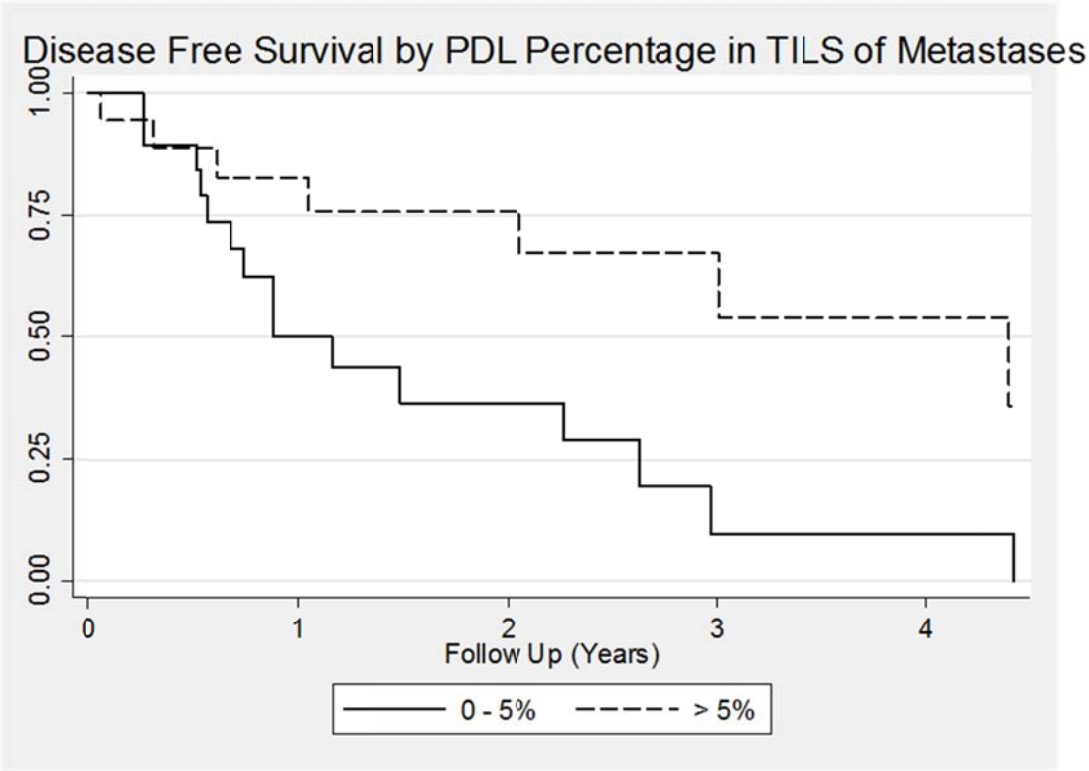
Table 5 – PD-L1 expression in primary HNcSCC tumor cells and matched metastases (n=38)		
	PD-L1 0-5% in metastases	PD-L1 > 5% in metastases
PD-L1 0-5% in primaries	16 (42.1%)	8 (21.1%)
PD-L1 > 5% in primaries	5 (13.2%)	9 (23.4%)

Figures


PD-L1 staining intensity
PD-L1 staining intensity 1+ in tumor cells
PD-L1 staining intensity 2+ in tumor cells
PD-L1 staining intensity 3+ in tumor cells
PD-L1 staining intensity 3+ in Tumor Infiltrating Lymphocytes


Disease Free Survival by PDL Percentage in Primary cSCC
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Follow Up (Years)
0 - 5%
> 5%


Disease Free Survival by PDL Percentage in Primary TILS
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Follow up (Years)
0 - 5%
> 5%


Disease Free Survival by PDL Percentage in TILS of Metastases
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Follow Up (Years)
0 - 5%
> 5%